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09/521,195	03/07/2000	Jun-ichi Nezu	06501-057001	9418

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EXAMINER
MERTZ, PREMA MARIA

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/521,195	Applicant(s) Nazu et al.
	Examiner Prema Mertz	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jun 10, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above, claim(s) 8-27 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-7 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Restriction/Election

1. Applicant's election with traverse of Group I (claims 1-7, 8) in Paper No.8 (7/30/01) is acknowledged. Claim 8 has been subsequently canceled in Paper No. 13 (3/29/02). The traversal is on the ground(s) that the restriction is improper since the examiner has not shown that examination of Groups I-II, would entail a serious burden. Applicants have also argued that both SEQ ID NO:1 (OCTN1) and SEQ ID NO:3 (OCTN2) are human transporter amino acid sequences classified in class 530, subclass 350, share 76% overall identity, and possess similar activity. This argument is non-persuasive because Group I is directed to a polypeptide of SEQ ID NO:1 and the special technical feature of this Group is the amino acid sequence of SEQ ID NO:1. Claims 1-7 are improper Markush claims because they do not meet unity of invention. The different elements of a Markush group must meet unity of invention. The other polypeptide (SEQ ID NO:3 listed in claim 1), does not share the special technical feature (SEQ ID NO:1) of Group I, because the other polypeptides (SEQ ID NO:3, 22 or 27) are structurally and functionally different. Furthermore, the nucleic acids (SEQ ID NO: 2, 4, 23, 28), each encoding the proteins of SEQ ID NO:1, 3, 22 or 27 are structurally and functionally different. Therefore, contrary to Applicants arguments, even though SEQ ID NO:1 and 3 share 76% overall identity, a search of the literature for the polypeptide of SEQ ID NO:1 would not necessarily be expected to reveal art regarding the polypeptide of SEQ ID NO:3, because the inventions are distinct and the searches are extensive requiring separate searches which would be unduly burdensome.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP... § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP... § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

Therefore, claims 1-7 will be examined only with respect to SEQ ID NO:1.

The Groups as delineated in the restriction requirement (Paper No. 6, 6/22/01) are patentably distinct one from the other such that each invention could, by itself, in principle, support its own separate patent (as shown by the arguments put forth in the written restriction requirement).

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8 (7/30/01).

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the claims be amended to recite "human transporter polypeptide".

Claim rejections-35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 1-4, 6-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth SEQ ID NO:1 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to variants of a polypeptide of SEQ ID NO:1, such variants being at least 70% identical, at least 80% identical, at least 95% identical and having upto 30 conservative substitutions in SEQ ID NO:2. Applicants disclose that mutant proteins which are obtained by altering the amino acids sequence of the transporter proteins of this invention by substitution, deletion or addition of amino acid residues are functionally equivalent to those of the transporter proteins of the instant invention (page 9, lines 22-30). Variants of the disclosed polypeptide may be naturally occurring allelic variants (see lines 20-23 on page 9) or non-naturally occurring variants (see lines 1-20, page 9). However, no disclosure, beyond the mere mention of variants is made in the specification. Furthermore, Applicants disclose that proteins functionally equivalent to the transporter proteins of the instant invention, can be obtained by isolating DNAs highly homologous to the DNA sequences encoding transporter proteins of this invention using hybridization techniques (see page 10, lines 13-21) This is insufficient to support the generic claims as provided by the Guidelines for the Examination of

Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Therefore only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. As a result, it does not appear that the inventors were in possession of variants of a polypeptide of amino acid sequence set forth in SEQ ID NO:1.

3b. Claims 1-4, 6-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially pure protein comprising the amino acid sequence set forth in SEQ ID NO:1, does not reasonably provide enablement for a substantially pure protein encoded by a nucleotide sequence hybridizing under stringent conditions to SEQ ID NO:2, as recited in claim 7, or for a substantially pure protein comprising the amino acid sequence at least 70%, 80%, 90%, 95% identical to the amino acid sequence set forth in SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Claims 1-4 and 7 are overly broad in their limitations of "70% identical", "80% identical", "90% identical", "95% identical" and " hybridizes under stringent conditions", respectively, because no guidance is provided as to which of the myriad of polynucleotide species encompassed by the claims will encode a polypeptide which retains the characteristics of a transporter of an organic cation, defined in the specification (pages 14-15). Variants of the polynucleotide can be generated by deletions, insertions, and substitutions, (page 9, lines 22-27), but Applicants have failed to disclose

any actual or prophetic examples on expected performance parameters of any of the possible muteins of the transporter protein molecule. Moreover, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the instant specification as to how one of skill in the art would generate a polynucleotide encoding a transporter polypeptide other than that exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any

necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim rejections-35 USC § 112, second paragraph

4. Claims 1-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites "hybridizes under stringent conditions", which is a relative term and renders the claim indefinite. Furthermore, some nucleic acids which might hybridize under conditions of moderate stringency, for example, would fail to hybridize at all under conditions of high stringency. The metes and bounds of the claim thus cannot be ascertained.

Claims 1-7 are vague and indefinite for reciting non-elected inventions corresponding to the polypeptides of amino acid sequence set forth in SEQ ID NO:3, 22 or 27. Appropriate correction is required.

Claim rejections-35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Koepsell et al. (U.S. Patent No. 6,063, 623).

The reference discloses a transport protein (see abstract) with 33.7% identity in about a 540 amino acid overlap with SEQ ID NO:1 of the protein claimed in the instant invention. A copy of the comparison of SEQ ID NO:1 of the polypeptide of the instant invention and the polypeptide disclosed in the reference is enclosed at the end of this action (SEQUENCE COMPARISON A). Therefore the DNA encoding the prtoein of the reference would be capable of hybridizing under stringent conditions to the polynucleotide of SEQ ID NO:2 described in the instant application. Therefore, the reference meets the limitations of claim 7.

Conclusion

No claims are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
August 8, 2002